Claim 44. A hybridoma capable of producing a monoclonal antibody as defined in Claim 42.

Claim 45. An immunoassay kit for measuring the blood level of a rapamycin comprising a monoclonal antibody as defined in any one of Claims 33, 34, 35, 36, 37, 38, 39 or 41.

Claim 46. An immunoassay kit for measuring the blood level of a rapamycin comprising a monoclonal antibody as defined in Claim 42. --

## REMARKS

Support for new Claims 41-46 can be found, *inter alia*, at page 12, line 19 to page 15, line 14 of the present specification. Hence, new Claims 41-46 do not constitute new matter, and thus entry is requested.

In paragraph 1, on page 2 of the Office Action, the Examiner has initialed the PTO-1449 Forms provided with Applicants' Information Disclosure Statement. However, the Examiner states that some of the references (i.e., Linskens et al, *Immun. in Plant Sci.*, pages 86-141 (1986); Holt et al, *Chem. Abst.*, Vol. 12, No. 25 (1994); EP 238,801; EP 487,289; EP 473,961; WO 90/06763; and U.S. Patents 5,138,051, 5,151,413, 5,169,773 and 5,122,511) were not included with the Information Disclosure Statement, and therefore she has not initialed these references.

The Examiner notes that upon receipt of copies of the missing references, she will consider them and provide Applicants with another copy of the initialed Forms PTO-1449.

Accordingly, Applicants submit herewith copies of the alleged missing references. The Examiner is requested to consider the same and provide Applicants with another copy of the initialed Forms PTO-1449 including the same.

In paragraph 4, on page 2 of the Office Action, the Examiner rejects Claims 33-40 under 35 U.S.C. § 112, second paragraph for reasons (a)-(b).

As to reason (a), the Examiner states that Claim 33 is unclear in use of the term "a rapamycin", since the Examiner contends that "rapamycin" is a single compound, and not a class of compounds.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

Applicants respectfully submit that, at the time of the present invention in 1993, the term "rapamycin" was well-known to be used in the art to refer generically to natural rapamycin and derivatives and analogs thereof (see, Claim 1 of European Patent 693132 B1, which has a priority date of April 8, 1993, which is of record, and which corresponds to U.S. Patent Publication 2002-0002273; see also, U.S. Patent 5,985,321, col. 4, lines 29 *et seq*; U.S. Patent 6,187,547, col. 1, lines 39-41, col. 4, lines 64-65, and col. 5, lines 10-11; U.S. Patent 6,083,521, col. 13, lines 7-9; and U.S. Patent 5,932,243, Abstract, and Claims 2 and 16, a copy of each of which is attached hereto). Indeed, U.S. Patent 5,897,990 even uses the expression "a rapamycin" in the claims thereof to generically refer to natural rapamycin and derivatives and analogs thereof

(see e.g., col. 1, lines 46-48 and Claims 2 and 16 thereof, a copy of which is attached hereto).

Furthermore, the present specification similarly uses the expression "rapamycins" generically to include to analogs and derivatives of natural rapamycin (see page 11, lines 28 *et seq* "This invention also covers analogous conjugates of other rapamycins, such as, but limited to ..."). Additional examples of such compounds are disclosed at page 12, lines 6 *et seq* of the present specification.

Thus, contrary to the Examiner's contention "rapamycin", in the context of the present application and the art, is not a single compound, but is a class of compounds including analogs and derivatives of natural rapamycin.

As to reason (b), the Examiner states that Claim 33 is unclear in the use of the expression "linking group", since the Examiner contends it is not clear what type of chemical moiety this group is and what it links to.

The Examiner is requested to note that Claim 33 recites that the linking group is at the 42-position or the 31-position of a rapamycin. It is clear from the present specification that the linking group is used to link to another moiety, for example, an immunogenic carrier material, such as those recited in Claim 37. Further, the particular linking group that is employed is not critical to the present invention. Numerous non-limiting examples of such linking groups are provided at page 4 of the present specification. Thus, it is improper for the Examiner to require Applicants to further define the linking group in independent Claim 33 (note, the linking group is

defined in dependent Claims 35-36 and 38). Nonetheless, in order to advance prosecution, Applicants hereby amend Claim 33 to indicate that the recited rapamycin molecule is conjugated to an immunogenic carrier material via said linking group. Support for this amendment can be found, *inter alia*, at page 3, lines 10 *et seq* of the present specification.

Accordingly, Applicants respectfully submit that the claims clearly and definitely recite the invention of interest, and thus request withdrawal of the Examiner's rejection.

In paragraph 6, on page 3 of the Office Action, the Examiner rejects Claim 33-40 under 35 U.S.C. § 103 as being unpatentable over Stella et al, Failli et al (A) ('203) and Failli et al (B) ('307), Kao et al ('678) and Kao ('477), Caufield and American Home Products in view of Sevier et al, Yelton et al or Campbell.

The Examiner contends that the primary references disclose pharmaceutically active rapamycin derivatives which are substituted at positions which correspond to either the 42- or 31-position (see Stella et al, Figure 1, column 1, lines 49-68; Failli et al (A), structure I; Kao et al, column 1, line 45-column 2, line 34; Kao, Abstract; Caufield, Abstract; American Home Products, title and Abstract; and Failli et al (B), Abstract). The Examiner acknowledges that none of these references teach the production of antibodies. However, the Examiner states that the secondary references teach that it is well-known in the art that monoclonal antibodies can be obtained to a wide variety of known antigens using conventional immunogenic hapten-carriers. Hence, the Examiner

concludes that it would have been obvious to substitute a rapamycin as a hapten in the conventional manner for preparing an immunogenic conjugate as described in the secondary references to achieve the present invention, citing *Ex parte Erlich*, 3 USPQ2d 1011 (Bd. Pat. App. and Int. 1986).

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

Initially, Applicants respectfully submit that at least with respect to Claims 39 and 40, i.e., the specifically deposited hybridoma and antibody, the Examiner has failed to establish a *prima facie* case of obviousness. Claim 39 is directed to the antibody which is produced by hybridoma RAP-42-OVAF$_2$#1hc (ATCC No. 11568); and Claim 40 is directed to hybridoma RAP-42-OVAF$_2$#1hc (ATCC No. 11568). None of the cited references alone or in combination teach or suggest this specific antibody/hybridoma.

As to Claims 33-38, the Examiner is requested to note Applicants are <u>not</u> claiming a hapten-conjugate *per se*. Rather, Applicants are claiming a monoclonal antibody. Thus, the basis of the Examiner's rejection, i.e., that it would have been obvious to substitute a rapamycin as a hapten in the conventional manner for preparing an immunogenic conjugate, is <u>not</u> legally proper.

Moreover, *Ex parte Erlich*, relied upon the Examiner to support her rejection, is simply <u>not</u> relevant to the present claims. In *Ex parte Erlich*, the claims were directed to monoclonal antibodies specific for <u>fibroblast</u> interferon. At the time, it was <u>known</u> in the prior art that both <u>fibroblast</u>

interferon and leukocyte interferon were antigenic, and that the technique of Kohler-Milstein for production of monoclonal antibodies had been successfully employed to leukocyte interferon to produce monoclonal antibodies specific for leukocyte interferon. The Board concluded it would have been obvious to one of ordinary skill in the art at to use the method of Kohler-Milstein to form monoclonal antibodies specific for fibroblast interferon since fibroblast interferon was also a known antigen.

However, contrary to the Examiner's apparent contention, rapamycins were not known antigens. In fact, in April 1993, rapamycins were thought in the art not to be antigenic/immunogenic (see, e.g., European Patent Publication 0693132, page 1, lines 19-22; of record). Hence, while it may be "obvious to try" the Kohler-Milstein technique as applied to a rapamycin, this is not the standard of obviousness under 35 U.S.C. 103 (*Ex parte Old*, 229 USPQ 196 (Bd. Pat. App. and Int. 1985)). As will be discussed in detail below, the references relied upon by the Examiner, do not provide a reasonable expectation of success.

Moreover, it is well-settled law that where the starting material is novel and unbovious, as are the recited conjugates, the use of the same must also be novel and unobvious (*In re Pleuddemann,* 15 USPQ2d 1738 (Fed. Cir. 1990); and *In re Ochiai*, 37 USPQ2d 1127 (Fed. Cir. 1995)). Applicants respectfully submit that the immunogens employed in the present invention to obtain the monoclonal antibody are both novel and unobvious.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested in any of the primary references alone or when combined with the teachings of any of the secondary references, and in any event the combination thereof can only be made in hindsight, which is legally improper. Thus, Applicants request withdrawal of the Examiner' rejection.

In paragraph 7, on page 4 of the Office Action, the Examiner rejects Claims 33-40 as being unpatentable over the primary and secondary references noted above in further view of Niwa et al.

Specifically, the Examiner states that Niwa et al teaches preparation of immunogens using FK-506, which the Examiner contends is similar to natural rapamycin, as a hapten, wherein a linker is used at the 42-position, as well as the production of monoclonal antibodies thereto. Hence, the Examiner concludes that in view of the teachings of Niwa et al, i.e., that monoclonal antibodies to allegedly structurally similar macrocylic compounds can be prepared using 42-substituted hapten/carrier conjugates, the presently claimed monoclonal antibodies would have been obvious to one of ordinary skill in the art.

At page 5 of the Office Action, the Examiner notes Applicants' arguments in the Preliminary Response filed August 30, 2000, that it was unpredictable that monoclonal antibodies could be generated against a rapamycin even though it was known that monoclonal antibodies could be generated against FK-506 of Niwa et al. However, the Examiner states that this argument is not persuasive because although the mechanism of

pharmaceutical action may be different for rapamycins and FK-506 of Niwa et al, the prior art cited in Applicants' Preliminary Response does not support the proposition that it would have been unexpected that monoclonal antibodies to rapamycins could be prepared, i.e., the Examiner contends that the cited prior art relates only to the general immunosuppressive effect of rapamycins and not the production of monoclonal antibodies specific for rapamycins.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

Again, initially, Applicants respectfully submit that at least with respect to Claims 39 and 40, i.e., the specifically deposited hybridoma and antibody, the Examiner has failed to establish a *prima facie* case of obviousness.

As to Claims 33-38, as clearly demonstrated in:

(1) the executed Declaration of Prof. Barrie W. Bycroft under 37 C.F.R. § 1.132 (with attachments) submitted herewith; and

(2) the unexecuted Declaration of Dr. Katherine Molnar-Kimber under 37 C.F.R. § 1.132 (with attachments) submitted herewith,[1/]

at the time of the present invention, in April of 1993, there was no reasonable expectation that one could successfully obtain monoclonal antibodies to rapamycins, even in view of the

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[1/] An executed Declaration (without attachments) will be submitted shortly.

teachings of Niwa et al of obtaining monoclonal antibodies to FK-506.

More specifically, at the time of the present invention in April 1993:

(a) it was known that some small drug conjugates had <u>failed</u> to generate monoclonal antibodies specific to the drug entity within the conjugate, and there was <u>little</u> rationale as to which structures in small molecule conjugates would be recognised by B cells to generate antibodies, other than a general understanding that molecules possessing regions of <u>conformational</u> <u>flexibility</u> (such as the rapamycin macrolide molecules) are <u>less</u> likely to be recognised by B cells, and therefore <u>less</u> likely to generate monoclonal antibodies (Bycroft Declaration, ¶¶14 and 31);

(b) the generation of monoclonal antibodies to potent immunosuppressive agents (such as rapamycins) was known to be difficult and unpredictable (Bycroft Declaration, ¶¶16-17 and 31);

(c) although monoclonal antibodies had been generated (with some difficulty) to FK-506:

(i) there are <u>substantial</u> structural differences between rapamycins and FK-506: unlike FK-506, (a) natural rapamycin contains a triene with its larger ring structure, and (b) the larger rapamycin molecules are

generally more conformationally flexible than the FK-506 molecule; and

(ii) rapamycins exhibit significantly different biological activities to FK-506 both at the cellular and the molecular level (Bycroft Declaration, ¶¶18-28 and 31);[2/]

(d) no monoclonal antibodies had been generated to an immunosuppressant that had the same mode of action as rapamycins at the cellular level (i.e., (i) blocked the proliferative response of T cells to the IL-2 signal and the T helper effect on B cells; and (ii) suppressed B cell activation and antibody production) (Bycroft Declaration, ¶¶18-25 and 31); and

(e) no monoclonal antibodies had been generated to an immunosuppressant that had the same mode of action as rapamycins at the molecular level (i.e., bound to FKBP and then to a target later identified as mTOR/FRAP/RAFT1) (Bycroft Declaration, ¶¶26 and 31).

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[2/] The rapamycin immunogen conjugates may not be immunosuppressive. However, it was known in April 1993 that the conjugates were likely to breakdown to the free active drug when injected into the animal due to non-specific esterases acting on the ester linkage between rapamycins and the carrier molecule in the immunogen conjugate (Bycroft Declaration, ¶¶29-30).

The production of monoclonal antibodies involves the activation of antigen presenting cells (APCs) and presentation of the antigen, activation of T cells and activation and differentiation of B cells. In April 1993 it was known that it is difficult to generate monoclonal antibodies to immunosuppressive agents. Since, in April 1993, rapamycins were known to be potent immunosuppressive agents, one of ordinary skill in the art would not have had any reasonable expectation of success in generating monoclonal antibodies to rapamycins (Molnar-Kimber Declaration, ¶¶30-31 and 46).

The fact that monoclonal antibodies had, with some difficulty, been generated to FK-506 does not change this. There are significant structural differences between FK-506 and rapamycins, and these result in divergent biological activities (Molnar-Kimber Declaration, ¶¶32 and 47).

At the cellular level, rapamycins and FK-506 differ in their effects on:

(i) the cellular response of T cells,

(ii) an enzyme involved in the regulation of the cell cycle of T cells,

(iii) activated macrophages, and

(iv) the humoral response, involving antibody production by B cells, e.g., FK-506 augments antibody production in some models, whereas rapamycins directly block antibody production from B cells (Molnar-Kimber Declaration, ¶¶33-41, 45 and 48).

At the molecular level, rapamycins and FK-506 differ in the effector proteins to which they bind and the molecular pathways which they target (Molnar-Kimber Declaration, ¶¶42-45 and 49).

Accordingly, rapamycins have a significantly different effect on the immune system and, in particular, on antibody production, compared to FK-506. Thus, one of ordinary skill in the art in April 1993 would not have reasonably predicted based on the teachings in Niwa et al that monoclonal antibodies to rapamycins could have been generated (Molnar-Kimber Declaration, ¶50).

Hence, absent hindsight, one skilled in the art would not have been motivated to combine the teachings of Niwa et al with respect to FK-506, with any other the references to achieve the present invention, i.e., at most, it would have merely been "obvious to try", which again is an improper basis for a rejection under 35 U.S.C. § 103 (*In re O'Farrell*, 7 USPQ2d 1673, 1680 (Fed. Cir. 1988)).

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested in any of the primary references cited by the Examiner either alone, or when combined with the teachings of any of the secondary references cited by the Examiner in view of Niwa et al, and in any event the combination thereof can only be made in hindsight, which is legally improper. Thus, Applicants request withdrawal of the Examiner's rejection.

Finally, Applicants would like to bring to the Examiner's attention U.S. Application 09/933,104, filed August 20, 2001, which was published on January 3, 2002 as No. 2002-0002273 (a Second Supplemental Information Disclosure Statement, along with

a PTO Form-1449 listing the same are submitted simultaneously herewith).

U.S. Application 09/933,104 is a Divisional of U.S. Patent Application No. 09/585,743, filed June 2, 2000, which is a Divisional of U.S. Patent Application No. 09/072,278, filed May 4, 1998 (now abandoned), which is a Continuation of U.S. Patent Application No. 08/532,837, filed October 5, 1995 (now abandoned), which is a Rule 371 of PCT/EP94/01006, filed March 30, 1994, which claims benefit of GB 9307491.2, filed April 8, 1993.

In the Preliminary Amendment field May 24, 2000, and the Information Disclosure Statement filed May 24, 2000, Applicants previously brought to the Examiner's attention U.S. Patent Application Serial No. 09/072,278, filed May 4, 1998, and, what is believed to be the European counterpart (European Patent 693132 B1, published January 24, 1996).

U.S. Publication No. 2002-0002273 contains claims to monoclonal antibodies specific for a rapamycin, a hybridoma producing the same, an immunoassay employing the same and an immunoconjugate used to produce the same.

In view of the amendments to the claims and arguments set forth above, reexamination, reconsideration and allowance are respectfully requested.

The Examiner is invited to contact the undersigned at his Washington telephone number on any questions which might arise.

Respectfully submitted,

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**A P P E N D I X**

Marked-Up Version of Changes

**IN THE CLAIMS:**

The claims are amended as follows:

Claim 33. (Amended) A monoclonal antibody having binding specificity for a rapamycin, wherein said antibody is obtained using an immunogen comprising a molecule selected from the group consisting of a rapamycin having a linking group at the 42 position, a rapamycin having a linking group at the 31 position, and a rapamycin having a linking group at both the 42 position and the 31 position, wherein said molecule is conjugated to an immunogenic carrier material via said linking group.

Claim 37. (Amended) The monoclonal antibody of Claim 33, wherein said [molecule is conjugated to an] immunogenic carrier material is a protein selected from the group consisting of keyhole limpet hemocyanin and ovalbumin.

New Claims 41-46 are being added.